Neuromodulation Therapies for Traumatic Brain Injury

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Abstract. Traumatic brain injury (TBI) is associated with high disability and death rates worldwide. Medically refractory patients could turn to neuromodulation therapies. Yet there were no essays focused on this review. This essay introduces two main neuromodulation theories, including their treatment principles and therapeutic effects. The mentioned theories were vagus nerve stimulation (VNS) and deep brain stimulation (DBS). VNS was proved to have a good performance in improving the consciousness of severe patients at the TBI early stage. It could also help reduce secondary brain injuries. While clinical research on DBS also proves a significant advantage in the recovery of minimally conscious state (MCS) patients, especially in the prolonged disorder of conscientiousness (DOC) patients. DBS also proves to be effective in improving the arousal mechanism of cognitive and motor function of re-waken patients, especially combined with rehabilitation treatments. The patient scenarios of these two neuromodulation methods were discussed, as were the advantages and limitations.

Keywords: Traumatic brain injury; vagus nerve stimulation; deep brain stimulation.

1. Introduction

TBI is a severe disease becoming an emerging threat for young people worldwide. It remains the most complex disease in the most complex organ. TBI is usually caused by penetrating and non-penetrating head injuries, leading to focal and diffuse traumatic brain injury. It could generate subdural and epidural hematomas and neuronal damage. Secondary injury would also happen, involving hypotension, hypoxia, and other vascular problems. These brain damage made patients die or have a disability, including DOC [1]. Tradition treatment would be drug delivery, for instance, opioids. However, drug treatment would not show identical therapeutic effects for medically refractory patients. It may cause substance use disorder, leading to tolerance development, drug addiction, or even overdose death [2].

Thus, neuromodulation treatments became a new trend in the TBI treatment area. Clinical neurophysiology has played a significant role in the clinical success of neuromodulation treatments. It helps shape the way of understanding neurons and change individual neuromodulation approaches. Neuromodulation theory often uses invasive or noninvasive micro-electrode with high impedance at a certain position to stimulate neurons and create different firing patterns by leaking out weak currents. It could also record the multiunit activity of neurons, providing electrophysiological images. In TBI, it includes electroencephalography to help doctors and researchers to judge the brain condition [3]. This article will mainly focus on two emerging technologies focusing on TBI treatments. Vagus nerve stimulation and deep brain stimulation therapy.

Vagus nerve stimulation, or VNS, is one of the neurosurgical treatments that use a generator and electrodes to stimulate the vagus nerve repeatedly, which is the tenth cranial nerve in charge of the connection between the brain and organs. The equipment of VNS is divided into additional implanted VNS, noninvasive VNS (nVNS), and newly developed transcutaneous VNS (tVNS). It was widely proved in animal research that VNS could improve various brain functions, including cognitive and motor functions [4]. It could also reduce secondary brain injury by providing anti-glutamate effects and anti-inflammatory activity. VNS could also help decrease acutely elevated intracranial pressure and spread depolarizations effectively [5]. Thus, it proves the effectiveness of applying VNS treatments at the early stage of TBI. Also, some research claims that VNS could also improve the consciousness state of some prolonged DOC patients [6]. Thus, VNS may help improve cognitive and motor recovery by promoting the increase of adrenergic, plasticity, and orexinergic neurotransmission [7].

DBS was used on patients with Parkinson's disease and essential tremors. However, DBS was also effective in TBI treatments as well. DBS usually uses stereotactic techniques, like implanting electrodes in subcortical brain areas. The electrodes could deliver several electrical pulse wave modes to the same brain area. For TBI, the beneficial stimulation areas are concentrated in the central thalamus area, which may be responsible for the arousal mechanism during the recovery of consciousness and cognitive function [8]. Several researchers claim that patients who were implanted with DBS one year after TBI improved their post-surgical outcome score measures after long-term stimulation. The reason for the improvement is that DBS could enhance the function of the undamaged neurons, which tend to be low-firing after TBI occurs, by activating action potentials along the axons of central thalamic neurons [8]. DBS is also proved effective in improving conscious patients' behavioural responsiveness and cognitive capacity, as the stimulated main thalamic area may affect the functional process of arousal regulation [9]. Combined with cognitive and sports rehabilitation, DBS improves TBI patients with DOC [10].

TBI is first introduced in this article, including the formation and danger. Also, the importance of neuromodulation methods for treating TBI is explained. Then, two commonly used neuromodulation methods are introduced: vagus nerve stimulation and deep brain stimulation. The treatment mechanism, development history, and research status of VNS and DBS were mainly introduced. Finally, a discussion of the specific patients' scenarios where these two methods would perform best. And the advantages and limitations of both approaches are listed. Assumptions and possibilities for developing VNS and DBS were also discussed in the end.

2. Neuromodulation therapies for traumatic brain injury

2.1. Traumatic brain injury

Young people's leading cause of death and disabilities is TBI. TBI is usually caused by head injuries, which could be divided into penetrating and non-penetrating types. Both head injuries could harm the brain, leading to focal and diffuse TBI. It could form subdural and epidural hematomas in the brain, as Fig. 1 shows, along with neuronal damage. Also, some primary injuries (like neurological damage) happen after the instant contacting head injuries, which could be called secondary injuries. Secondary brain injury develops over time, which is the important factor that hospitals mainly concentrate on after TBI. Brain swelling is one of the most critical factors causing subsequent damage. There are vital risks in severe TBI patients that lead to comatose or even death, including diverse focal hemorrhagic brain lesions, diffuse axonal damage, and later extensive disruption of neuronal connections. If not avoided or appropriately managed, these symptoms aggravate brain damage and reduce the possibility of survival. Patients with severe TBI frequently exhibit diminished consciousness due to the decreased neural connection between arousal and awareness–controlling areas. The cortico-cortical and thalamocortical networks were also disrupted in such areas.

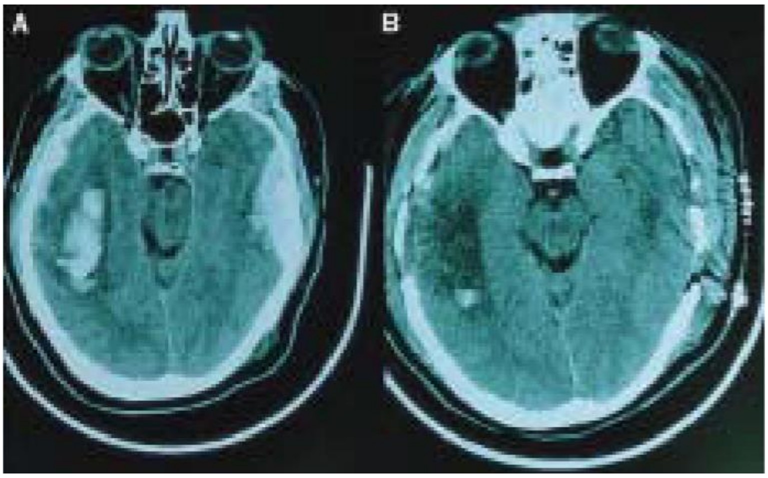

Fig 1. Computed tomography images of a TBI patient before and after the surgery [1].

As severe TBI mainly causes the long-time disability in young people, it is gradually becoming an important social and economic issue. Severe TBI may cause a DOC, resulting in the patients' persistent unconscious state. Two neural systems in the brain control the waken mechanism: awareness and arousal systems. Both could lead to DOC if disturbed. DOC could be categorized into a coma, vegetative state (VS), and MCS. The classification criteria are set by observing patients' behaviors [1].

It is sad to say that some severe patients may remain in VS or MCS infinitely. For some TBI patients who may finally turn back to a conscious state, however, they may not move through the DOC states in a specific order before they come to awaken. Thus, sometimes in patients suffering from grievous brain injury, it is hard to define their state. Several mark systems were invented to judge the conscious state of the patients in more detail. The normally used systems were the Glasgow coma score (GCS), Coma recovery scale and near coma scale. For instance, the degree of awareness of GCS could be divided into mild, moderate, and severe, or panel during the resuscitation process. Patients with the least mild TBI could be scored as 13-15 using GCS. This means that short–term memory problems and focus issues would happen in most cases. Also, there is a high possibility of neurological recovery in such patients. Patients scored as GCS 9 -13 are also mild TBI patients but with worse symptoms like stuporous or lethargy. Patients with GCS 3-8 are even worse. They could barely open their eyes even following instructions after severe brain injuries [10].

Immediate treatment for TBI would be adequate cerebral perfusion surgery and intracranial pressure monitoring right after patients send to the hospital. Traditional therapy like drug delivery was used for prolonged comatose TBI patients. However, drug treatments would not show identical therapeutic effects for some patients. It may even cause substance use disorder, like tolerance development, drug addiction, or even overdose death [2]. Thus, neuromodulation treatments with medical micro-electrode devices became a new trend in the TBI treatment area. Two primary therapies were introduced in the following content.

2.2. Vagus nerve stimulation for traumatic brain injury

The vagus nerve is the tenth cranial nerve, which has branches in the neck, thoracic, and abdominal cavity. It has fibers that allow the brain and internal organs to communicate through signal transmission. 80 percent of the total vagus nerves are afferent connection fibers, which all end in a specific area in the brainstem called nucleus tractus solitarius. The vagus nerve could activate the basal forebrain cholinergic system and the locus coeruleus norepinephrine system by giving electrical stimulation, which could lead to the release of neurotransmitters in the cerebral cortex [7].

VNS therapy was firstly performed on humans in 1988, and the effects of this therapy were randomly discovered after long-time animal experiments [4]. When medicine and epileptic surgery failed to control seizures in a patient, the use of VNS was finally approved in 1997. Also, VNS was approved as a complementary therapy for treating major depressive disorders in 2005. Additionally, it has been reported that numerous current clinical trials utilize VNS for numerous disorders, such as Alzheimer's disease, congestive heart failure, and stroke.

It has been suggested that VNS may be used therapeutically to treat acute brain ailments such as TBI and stroke. Scientists wanted to help the neurons recover and survive after realizing that TBI could not only cause intense harm. Preclinical models of TBI have been used to study the therapeutic impact of VNS. These research findings demonstrated that VNS enhanced several mental processes in the patient model with TBI, including the improvement of cognitive and motor outcomes. VNS was also proved to help to decrease in secondary brain injury.

Four key articles, which were published by one group, showed that VNS could mediate recovery in models of rats with TBI by following the fluid percussion model, as evident in improvements in motor and cognitive function, decreased cortical edema, and neuroprotective effects. The authors attributed the elusive underlying mechanisms to the reduction of post-traumatic seizures due to a noradrenergic mechanism and some unknown mechanisms [5]. Reviewing and expanding upon these concepts, it could be hypothesized that additional potential mechanisms may be involved as VNS could also help reduce peri-infarct depolarizations and glutamate-mediated excitotoxicity. It may also improve the stabilization of intracranial pressure and enhance synaptic plasticity. The upregulation of endogenous neurogenesis and anti-inflammatory effects would also occur in the VNS treatment process [4].

Although potential clinical uses for VNS in TBI patients had been suggested in the past, these uses are still currently unclear. In one case report, VNS was used to treat a patient who had been in VS for 15 years due to TBI. Before and after the VNS was implanted, electroencephalography and F-18 fluorodeoxyglucose Positron emission tomography scans were performed, and a log of daily activities was kept. After one month of stimulation, the study's findings indicated improvements in patients with full arousal. The patients could complete tests like sustained attention, bodily movement, and visual tracking. Coma Recovery Scales-Revised scores of these patients were increased to 10 from 5, demonstrating a shift from VS to MCS.

Though VNS has several advantages in TBI models, its intrusive nature makes it challenging to perform on TBI patients in an emergency. Thus, VNS may not have the most significant impact if it could not implant electrodes in patients right after TBI happens. Additionally, general anesthesia is required for TBI patients to implant the VNS devices with electrodes and batteries. Scar tissue forms everywhere around the electrode, making it barely possible to remove it during complications.

Fig 2. tVNS devices NEMOS placed at the left ear [12].

nVNS have been created recently to address this issue. Yang et al. showed that Blood-brain barrier integrity could be protected from damage brought on by ischemic stroke by noninvasive cervical VNS [7]. There was new research on nVNS technologies arising, as Fig. 2 shows. The cymbal conchae in the outer ears, which are innervated by the superficial auricular branch of the vagus nerve, are the target of tVNS, a novel kind of nVNS. VNS implantation surgical problems can be lessened using tVNS. It applies to ambulatory settings. tVNS is simpler to terminate and delete when a VNS application is not responding.

A small number of patients have been effectively exposed to tVNS thanks to Hakon and colleagues [11]. The tVNS devices used in their experiment are called 'Nemos', as shown in Fig 3. The authors treated 5 patients with severe TBI for 8 weeks using a 4-hour daily tVNS procedure. The ratings from the CRS-R after tVNS indicated that three out of the five patients had improved levels of consciousness. Moreover, during stimulation, tVNS exhibited no negative impacts on any physiological variables, such as pulse rate or blood pressure.

2.3. Deep brain stimulation for traumatic brain injury

Brain stimulation was first used to treat stroke by improving functional motor recovery. The studies were first performed on a cortical brain area in rodents and some primate animals. The effects would be even better if combing motor recovery training with cortical stimulation. Then in the 1960s, the possibility of improving the arousal mechanism in patients with brain damage using electrical stimulation through 20 years of clinical experiments. The researchers found that if stimulated the reticular formation, midbrain tegmentum, pontine, and intralaminar thalamus in lab cats, the electroencephalogram shows rapid discharges in low-voltage, and the synchronization would also be lost. In the history of brain research, it has been hypothesized that providing electrical pulses in the anterior forebrain microcircuit could activate the decreasing synaptic activity. It could also help change the arousal-managed systems and improve the cognitive mediated activities [9].

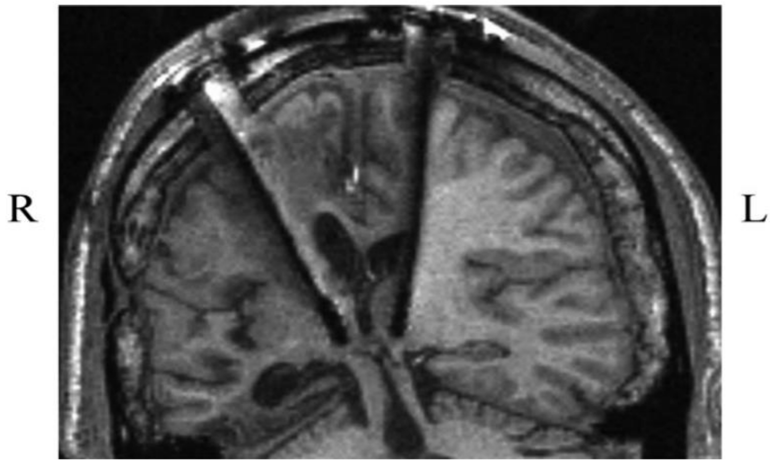

Fig 3. Electrode leads implanted in the central thalamus of the brain [9]

Such a theory is called DBS. It has been proved that DBS could effectively treat movement disorders and some mental diseases. DBS also succeeded in experiments in treating diseases like Parkinson's and essential tremors. However, there is less research on how DBS works in TBI than strokes or movement disorders. The most important component of DBS is an electrode lead located in a special area of the brain, as Fig. 3 shows. Thus, the implanted electrodes could leak some electricity around the located spot at a small amount, sending electrical waves to specific areas in the brain. There are still some controversies about the working mechanism of the DBS theory. However, the effects of electrical pulses were approved, including modulation of neuron activity at the local spot, and changing the neuronal activities, which may be linked with some diseases at the end of the path [12].

DBS showed a strong possibility of improving motor function in TBI patients based on preclinical research and human experiments. The pallid thalamic tract and the verbal lobar region of the anterior cerebellar lobe were the mostly stimulated area in DBS treatments [14]. Numerous studies have suggested that the anterior forebrain microcircuit is important for consciousness and cognitive function. It is located at the central thalamus, which could help recovery naturally and result from treatment after brain injury. It is stated in the former part that most of the investigation focused on the thalamus stimulation in DBS. However, in some studies, they turned to the medial vermal lobe, which is located in the anterior cerebellar lobe, which also proved useful. The necessity for prompt delivery (minutes, hours, or days after injury) may restrict the effectiveness of safe and efficient neuroprotective treatments. There will still be a need for rehabilitation therapy that can speed recovery. By promoting brain regeneration and remodeling, rehabilitation therapy combined with DBS treatment seek to restore motor function. The augmentation of rehabilitation therapies demonstrates the potential for boosting behavioral outcomes and expanding the window of opportunity for effective treatment [10].

Despite the fact that the underlying neurological underpinnings of disorders of consciousness in TBI are still not fully understood, the application of DBS on various targets to assist recovery in individuals with such diseases has yielded diverse results.

In some TBI cases, a study by Magrassi et al. claimed that their patients' CRS-R score was increased from 14 to 15. Still, they could not give delightful performances like consistent, communicative behavior. Still, one patient showed no improvement after stimulation in the same research. A study by Chudy et al. reported that a female patient recovered from a coma state. The near coma scale of these patients showed the improvement of cognitive function to 0 from 1.6/1. She could follow some simple instruments but remained to stay in a wheelchair. In Galanda's research, their patient was recorded to be able to walk with an assistant and feed himself after the DBS treatment without any validated outcome measures. Lemaire's study revealed that all their male patient's overall CRS-R score had improved statistically significantly during and after his one-and-a-half-month ON period DBS. However, the CRS-R score improvement was insignificant for female patients after the intervention. In a series of single case examinations, Schiff et al. found that the ON and OFF stimulation periods could also prove effective. All six CSR-R sub-scores of the TBI patients had been increased as compared to presurgical baseline scores. Three sub-scores, namely, arousal, oral eating, and limb control, all demonstrated a considerable improvement due to the stimulation of the central thalamus during the crossover phase. Regarding side effects, a scopolamine patch was advised for vomiting during the first month of the DBS ON phase. Such procedure also should be performed in the sixth month of the DBS OFF periods [8].

3. Discussion

Neuromodulation theory treatments are helpful for TBI patients with DOC, especially for medically refractory patients. Two theories were useful in clinical cases: VNS and DBS. VNS theory aims to use implanted or wearable electrodes to excite the vagus nerve, which has afferent and efferent fibers that allow communications between the brain and internal organs. DBS theory also uses electrodes, which tend to stimulate the anterior forebrain microcircuit, especially the central thalamus, which is significant in arousal from loss of consciousness and cognitive function. Both theories significantly impact the recovery of severe TBI patients with DOC. However, the application scenarios of these two technologies, which may have their biggest impacts, have not been discussed before. Also, the advantages and limitations of the therapies will be discussed in this article. Finally, hypotheses and prospects for further developing the two technologies were made.

Dong and Feng's research has proved that VNS could achieve the best results if it could be performed after the TBI happens as soon as possible. Several groups of rats were processed to TBI in this study. However, the group that applies VNS one hour after the injury shows the greatest increase in the number of re-awake rats [13]. Also, research proves that VNS could improve secondary diseases and reduce the following harm to the brain. Thus, the specific group of patients who need VNS the most should be early-stage TBI patients. VNS can reduce other brain injury symptoms and allow patients to recover cognitive and motor function as soon as possible.

For DBS, the applicable patients should be patients with severe TBI in prolonged coma. First, in terms of the stimulation mechanism of DBS, the stimulated part is the central thalamus area, which can coordinate different areas, mainly the arousal function. Thus, in many cases, deep brain stimulation has been greatly performed in MCS/VS patients. Research claims that even 20-year TBI patients with DOC could improve the consensus state [8]. DBS also works when it comes to reawakened conscious patients. DBS would help regulate the arousal mechanism in different regions responsible for cognitive and motor recovery. If combined with rehabilitation trains, the results are even better. Also, more vital areas for improving DOC in patients with TBI are being explored. For example, studies have shown that stimuli against the Lateral Hypothalamic Area [14] and the lateral cerebellar nucleus have also been shown to be effective for TBI [13] but are currently only in the experimental animal stage.

VNS and DBS each have advantages and limitations. First, the biggest advantage of VNS is that it can reduce subsequent brain damage, which means that if VNS can be directly surgically installed when the patient is sent to the hospital, it is the fastest way to recover. But the article also pointed out that installing an implantable VNS in a patient who has just suffered from TBI is basically impossible. Considering the injury of the patient and the possible damage to the skull, this makes the implantable VNS less effective. Of course, a newly published article mentions that long-term stimulation of non-implantable VNS devices can also play a positive role in patients. It reveals an exciting research direction and, if proved feasible, will compensate for the inability of VNS to the inconvenience of installation during the best treatment period. It will undoubtedly make the VNS lead a more significant role in TBI treatment. DBS's role is to stimulate the thalamic region deep in the brain to promote awakening the patient's consciousness, which is a huge advantage in treating long-term comatose patients. Of course, in the study of VNS, there are also cases of improving the coma index for 15-year-old patients, but articles do not specify how much VNS has played a role. For DBS, another advantage is that it can promote the recovery and treatment of newly awake TBI patients. Some cases show that if combined with exercise rehabilitation, it greatly affects the initial recovery of motor motion. After all, DBS is also commonly used in the treatment of movement disorders [12]. Of course, the disadvantage of DBS is that it costs a lot. An article on economic effectiveness mentioned that if not for drug-refractory patients or drug intolerance, DBS would not be chosen first. Compared with traditional drug treatments, the cost of DBS is huge, almost two to three that of drug treatments [15]. Suppose there is also a noninvasive, wearable DBS treatment that can have the same effect. In that case, it will greatly promote the development of DBS, and patients may no longer live in expensive wards and do not need implantation surgery.

4. Conclusion

VNS is more suitable to apply in the early-stage treatments of TBI patients. It can reduce the occurrence of secondary brain injury. Research on non-implantable tVNS has a great role in achieving that VNS is used in patients as much as possible after TBI has occurred, which allows the treatment of VNS to have better results and wider applications. DBS performs better in the conscious recovery of long-term DOC patients and newly awakened TBI patients who need improvements in cognitive and motor function. Researchers could focus on wearable DBS research, which is vital for decreasing the cost of DBS and improving the rate of use among patients.

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